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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,413	03/30/2001	Shigeru Yamamoto	Q63731	8678

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SAK

Office Action Summary	Application No.	Applicant(s)	
	09/806,413	YAMAMOTO ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,11,13,14 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *4 and 22* is/are allowed.

6)☒ Claim(s) *1-3,11,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 17, 2003, has been entered.

[2] Claims 1-4, 11, 13-14, and 22 are pending in the application.

[3] Applicants' amendment to the claims filed October 17, 2003, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims in the instant application.

[4] Applicants' arguments filed October 15, 2003 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Specification/Informalities

[6] The use of trademarks has been noted in this application (see page 26, lines 17, 18, 20, 21, and 25). They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 101

[7] Claim 3 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is drawn to a variant of SEQ ID NO:8. However, it is unclear as to whether the variant is naturally occurring or is "man-made", *e.g.,* generated by site-directed mutagenesis. Thus, the claim reads on a product of nature and should be amended to indicate the hand of the inventor, *e.g.,* by insertion of "purified" or "isolated". See MPEP § 2105.

Claim Rejections - 35 USC § 112, Second Paragraph

[8] In view of applicants' amendment to claims 1-2 and 11, the rejection of claims 1-2 and 11-14 under 35 USC § 112, second paragraph, as set forth in item 2, parts a-b in the Office action mailed January 10, 2003, is withdrawn.

[9] Claim(s) 1-2, 11, and 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 (claim 2 dependent therefrom) and 11 (claims 13-14 dependent therefrom) are confusing in the recitation of "the microorganism is selected from" followed by a listing of a plurality of microorganisms from which a single polypeptide is isolated. It is unclear as to how a single polypeptide can simultaneously be isolated from all of the recited organisms. It is suggested that applicant clarify the meaning of the claim by, for example, replacing "and" at the last line of claims 1 and 11 to "or" OR by inserting "the group consisting of" following "is selected from".

Claim Rejections - 35 USC § 112, First Paragraph

[10] The new matter rejection of claims 1-2, 11, and 13-14 under 35 USC § 112, first paragraph, as set forth in item 3 in the Office action mailed January 10, 2003, is maintained. Applicants argue the claims have been amended to recite "pH 2.5 to 3" instead of "pH 3 or less". Applicants argue this limitation is supported by the instant specification. To the extent the claims were rejected for reciting the limitation of "pH 3 or less", the rejection is withdrawn. However, due to newly added limitations in the claims, the rejection is maintained as follows.

Claims 1 (claim 2 dependent therefrom) and 11 (claims 13-14 dependent therefrom) recite the limitations of a molecular weight range of "about 47 kDa to about 51 kDa" (claims 1 and 11) and culturing performed at a "pH in a range of 5-6" (claim 11). Regarding the former limitation, the examiner acknowledges support in the specification for a polypeptide having a MW of 47 kDa (page 47, top of the specification) and support for a polypeptide having a MW of 51 kDa by calculation of MW by adding the MWs of

individual amino acids of SEQ ID NO:8. However, the examiner can find no support in the specification, claims, or drawings as originally filed for a polypeptide having a MW in the range of 47-51 kDa. Regarding the latter limitation, the examiner can find no support in the specification, claims, or drawings as originally filed for culture conditions in a pH ranging from 5-6.

Also, claim 2 recites the limitation of glycosides selected from beta-primeveroside, rutinose, gentobiose, arabinofuranosyl, and aviofuranosyl. Applicants state in the amendment filed October 17, 2003 that support for these glycosides may be found at page 6, lines 21-22 of the specification. The examiner acknowledges support in the specification for the glycosides of beta-primeverosidase (*e.g.,* page 6, bottom), gentobiose (*e.g.,* page 14, top), and arabinofuranosyl (*e.g.,* page 6, bottom). However, the examiner can find no support in the specification, claims, or drawings as originally filed for the glycosides of rutinose and aviofuranosyl.

Applicants are invited to direct the examiner's attention to the specification wherein these specific limitations are disclosed.

[11] Claims 1-3, 11, and 13-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention.

The claims are drawn to a genus of polypeptides isolated from a microorganism having the following characteristics: i) having the ability to release saccharides from a

disaccharide glycoside in a disaccharide unit, wherein said disaccharide glycoside has a glucose moiety at the aglycon side; ii) has enzymatic activity at pH 2.5-3; iii) is stable at 50 degrees Celsius or less; iv) has an approximate molecular weight (MW) in the range of 47-51 kDa; v) and is isolated from the genus *Aspergillus, Penicillium, Rhizopus, Rhizomucor, Talaromyces, Mortierella, Cryptococcus, Microbacterium, Corynebacterium, and Actinoplanes*, a method for producing same, and variants of said polypeptides.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the genus of claimed polypeptides, *i.e.*, the polypeptide of SEQ ID NO:8, isolated from *Aspergillus fumigatus*. The specification fails to describe any additional representative species of the claimed genus. It is noted that the

specification discloses that individual species of the genera of microorganisms recited in the claims exhibit production of a diglycosidase polypeptide (see Example 5, pages 35-45). The specification further describes physicochemical characteristics of diglycosidase from these microorganisms (pages 49-50). However, there is no disclosure of the MWs of diglycosidase enzymes isolated from the recited microorganisms and there is no evidence of record that would suggest that these microorganisms produce a diglycosidase that is similar in MW to *Aspergillus fumigatus* diglycosidase of SEQ ID NO:8. MPEP § 2163 states, "[i]f the application as filed does not disclose the complete structure (or acts of a process) of the claimed invention as a whole, determine whether the specification discloses other relevant identifying characteristics sufficient to describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention". In the instant case, the relevant identifying characteristics of the polypeptide of SEQ ID NO:8, isolated from *Aspergillus fumigatus,* are insufficient to describe the entire genus, particularly in view of the absence of any identifying MWs for the diglycosidases from microorganisms other than *Aspergillus fumigatus.* Also, the claims encompass a genus of polypeptides and variants having the ability to release saccharides from a disaccharide glycoside in a disaccharide unit, wherein said disaccharide glycoside has a glucose moiety at the aglycon side. This "function" encompasses widely variant diglycosidase enzymatic activities including activities other than beta-primeverosidase activity, *e.g.,* rutinosidase enzymatic activity. The specification indicates that the disclosed polypeptide has ability to hydrolyze beta-linked disaccharides and beta-glycosides. However, the specification

provides no indication that the disclosed polypeptide has the ability to hydrolyze *any* disaccharide to release a saccharide. As such, the function of the genus of claimed/recited polypeptides encompasses activities that are widely variant. Therefore, the claims encompass species having widely variant structures and/or functions and, as previously stated, the single disclosed species of the genus of claimed/recited polypeptides, *i.e.,* SEQ ID NO:8, fails to represent the entire genus. Given the lack of description of a representative number of polynucleotides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[12] Claims 1-3, 11, and 13-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO:8 and a method for making same, does not reasonably provide enablement for all polypeptides having the recited characteristics and being isolated from any microorganism isolated from the recited genera and a method for making same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.

1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass *all* polypeptides having the characteristics recited in the claims and being isolated from any species of the genera of microorganisms recited in the claims. In this case, the claims encompass polypeptides having a variety of enzymatic activities other than beta-primeverosidase activity, *e.g.,* rutinosidase activity. The specification indicates that the disclosed polypeptide only has ability to hydrolyze beta-linked disaccharides and beta-glycosides and does not have the ability to hydrolyze any disaccharide to release a saccharide. As such, the function of the genus of claimed/recited polypeptides encompasses a broad scope of enzymatic activities. In the instant case, the disclosure is limited to the polypeptide of SEQ ID NO:8 (being isolated from *Aspergillus fumigatus*) having beta-primeverosidase activity and a method for making same.

- The lack of guidance and working examples: The specification provides only a single working example of a polypeptide which meets the criteria set forth in the claims: *i.e.,* SEQ ID NO:8 having beta-primeverosidase enzymatic activity and a method for making same. This working example fails to provide the necessary guidance for making

the entire scope of claimed polypeptides. In this case, the specification fails to provide guidance regarding methods for isolating other diglycosidase polypeptides from microorganisms other than *Aspergillus fumigatus.* Furthermore, regarding claim 3, the specification fails to provide guidance for those nucleotides of SEQ ID NO:7 or amino acids of SEQ ID NO:8 that may be altered by substitution, addition, insertion, and/or deletion with an expectation of maintaining the desired enzymatic activity.

- The high degree of unpredictability: The specification sets forth a purification scheme for purifying the polypeptide of SEQ ID NO:8, being isolated from *Aspergillus fumigatus.* This purification scheme is dependent upon the amino acid composition and MW of the polypeptide of SEQ ID NO:8 and it is highly unpredicatable as to whether a similar purification scheme can be applied to other diglycosidases to obtain a similar result, *i.e.,* an isolated diglycosidase, particularly in view of the absence of characteristics of diglycosidases from other microorganisms that will aid in their isolation, *e.g.,* MW. Neither the prior art nor the specification provides any evidence that diglycosidases are highly conserved and/or have similar MWs, and it is highly unpredictable that the structure and/or MW of one working example, *i.e.,* the polypeptide of SEQ ID NO:8 (being isolated from (*Aspergillus fumigatus*), is/are representative of all others encompassed by the scope of the claims, such that these additional polypeptides can be isolated using similar methods. For example, Narikawa et al. (*Biosci Biotechnol Biochem* 64:1317-1319) describe a rutinosidase isolated from *Penicillium rugulosum* that is a tetramer having a MW of 245 kDa and a subunit MW of 65 kDa (1318, right column, top). Furthermore, regarding claim 3, predictability of which

changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within an amino acid sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. The state of the art provides evidence for the high degree of unpredictability in altering a polynucleotide sequence with an expectation that the encoded polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). While it is acknowledged that this reference was published in 1991, to date there remains no certain method for reasonably predicting the effects of even a *single* amino acid mutation on a protein. Such mutations may even completely alter a protein's activity.

- The amount of experimentation required is undue: While methods of isolating a polypeptide are known, it is not routine in the art to devise purification schemes for all

polypeptides having the structures, activities, and/or MWs isolated from all other organisms as encompassed by the instant claims. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

[13] Status of the claims:

- Claims 1-4, 11, 13-14, and 22 are pending.
- Claims 1-3, 11, and 13-14 are rejected.
- Claims 4 and 22 are in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's

supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

01-05-04

DAVID STEADMAN
PATENT EXAMINER